Differences in the Reporting Rates of Serious Allergic Adverse Events From Intravenous Iron by Country and Population

George R. Bailie, PharmD, PhD, and Jan-Jaap Verhoef

Abstract: Background: Previous studies have compared rates of adverse events between intravenous (IV) iron preparations; however, there has been no comparison of adverse event rates by country and population. Objectives: To compare rates of adverse events to IV iron products by country and population. Methods: All adverse events reported from 18 countries from January 1, 2003 to June 30, 2009 were obtained for iron dextran (ID), iron sucrose (IS), IS similars (ISS), and sodium ferric gluconate (FG). Rates of all adverse events and serious adverse events (anaphylaxis plus other serious allergic reactions) were calculated as number of events per gram of iron sold (gFe) per million inhabitants (mil) × 10⁻³. Odds ratios (ORs) were calculated for the risks of adverse events between products. Results: Iron use ranged from 1 gFe/mil (Poland) to 48,674 gFe/mil (Italy). Rates of all adverse events (reports/gFe/mil × 10⁻³) varied: for IS, it ranged from 0 (Poland, Austria, Czech Republic) to 1,222 (Ireland); for FG, from 3.3 (Czech Republic) to 183.6 (United States); for ID, from 0.9 (Turkey) to 46,875 (Switzerland). There were no reports of adverse events in ISS. In a subset of countries that used 2 or more iron products and had more than 1 serious adverse event, rates (reports/gFe/mil × 10⁻³) of all adverse events and serious adverse events were lowest for IS (39.8 and 1.7), intermediate for FG (54.8 and 4.5), and greatest for ID (337.7 and 20.5). IS had lower risks for all adverse events (OR, 0.63; P <.0001) and serious adverse events (OR, 0.31; P =.001) versus FG, and for all adverse events (OR, 0.13; P <.0001) and serious adverse events (OR, 0.07; P <.0001) versus ID. FG had lower risks for all adverse events (OR, 0.20; P <.0001) and serious adverse events (OR, 0.24; P <.0001) versus ID. Conclusions: Considerable international variation existed in the extent and choice of iron product and adverse event reporting, suggesting under-reporting in some instances. Clinicians should appreciate the differential risks between available products, and should critically review local reporting practices.

Introduction

The use of intravenous (IV) iron has been growing over the last decade, probably as a result of a better understanding of the appro-
ropriate management of moderate to severe anemia that is associated with numerous conditions, such as chronic kidney disease, pregnancy and the postpartum period, heavy uterine bleeding, inflammatory bowel diseases, bariatric surgery, chronic heart failure, oncology and chemotherapy-induced anemia, and elective surgery.\textsuperscript{1-9} It has become increasingly clear that judicious use of IV iron can optimize anemia management, reduce the need for erythropoiesis-stimulating agents and red cell transfusions, and reduce costs.\textsuperscript{10-13}

IV iron has the potential to cause allergic reactions, but the relative risks of these adverse events differs by agent.\textsuperscript{14-17} Recent papers have indicated that of the IV iron products studied, the highest risk for spontaneous reports of anaphylaxis and other serious allergic reactions (eg, bronchospasm, circulatory collapse, loss of consciousness) occurs with iron dextran (both high-molecular-weight and low-molecular-weight products).\textsuperscript{14-17} Further, there appears to be a difference in the rates of these adverse events between countries in Europe and North America.\textsuperscript{17} Because of the growing use of IV iron preparations worldwide, the administration to an ever-broadening scope of patient populations, and the introduction of newer agents (eg, generics and similars) onto the market, it is likely that the rates of reported adverse events will continue to increase.

Previous studies have compared reports of serious adverse events within a country between products based on rates of reported events. There has never been a comparison of relative rates for serious adverse events by country and by population at risk of receiving an IV iron product. Such an evaluation should be able to further identify trends in adverse events and reporting practices by country and might identify possible issues of either over- or under-reporting. We hypothesize that there will be large differences in the rates of adverse events, including serious allergic adverse events by product, when standardized to population.

**Methods**

We used data that had been collected and published in an earlier analysis.\textsuperscript{17} Briefly, all IV iron-related adverse events that had been reported to the World Health Organization (WHO) from 16 European countries (Austria, Czech Republic, Denmark, Estonia, Finland, France, Germany, Ireland, Italy, Norway, Poland, Spain, Sweden, Switzerland, Turkey, and United Kingdom) and North America (United States and Canada) from the first quarter of 2003 through the second quarter of 2009 were obtained from the Uppsala Monitoring Centre in Sweden. For the current analysis, we examined data for iron dextran, iron sucrose, iron sucrose similars (ie, “generic” iron sucrose products other than the originator product), and sodium ferric gluconate. Ferumoxytol, ferric carboxymaltose, and generic sodium ferric gluconate were not included in this study because they were either unavailable during the study period or had very recently been brought to the market. In North America, both high- and low-molecular-weight iron dextran formulations were available; reports for both were combined with reports that did not specify the type of formulation. Only low-molecular-weight iron dextran was used in Europe, and comparisons were made with the combined iron dextran in North America. For each iron product, data were obtained for all adverse events and for serious allergic adverse events. All adverse events were defined as the total number of adverse events associated with the products. Serious allergic adverse events were defined as anaphylaxis plus other serious allergic reactions. Anaphylaxis was defined using the WHO’s Adverse Reaction Terminology standardized coding system. Other serious allergic reactions were classified as any other events where the reports included any terms or codes for systemic allergy (ie, bronchospasm, circulatory collapse, dyspnea, hypotension or decreased blood pressure, laryngeal or laryngotracheal edema, loss of consciousness, oropharyngeal swelling, pharyngeal edema, stridor, syncope, or tongue edema) combined with any term or code with cutaneous evidence of bradykinin or histamine release (ie, angioedema, urticaria, idiopathic urticaria, injection site urticaria, populur urticaria, or urticaria vesiculosa).

IV iron sales data were purchased from IMS Health (Hersiswil, Switzerland), and the quantities converted into 100 mg dose equivalents (DEq) of iron. Iron use for each country was calculated as the total number of

\[ \text{Rates of serious adverse events (anaphylaxis and other serious adverse reactions) per gram of iron per million inhabitants per year in 2003–2009, by IV iron product and continent.} \]

**Note:** In Europe, only low-molecular-weight iron dextran is available; in North America, data are combined for both high-molecular-weight and low-molecular-weight iron dextran products.

*FG=sodium ferric gluconate; ID=iron dextran*; IS=iron sucrose.

\[ \text{Figure 1. Rates of serious adverse events (anaphylaxis and other serious adverse reactions) per gram of iron per million inhabitants per year in 2003–2009, by IV iron product and continent.} \]
grams of iron sold per million inhabitants over the entire 6.5-year period (gFe/mil). Country populations were determined from census reports from the Population Reference Bureau (www.prb.org) from 2006 (midpoint of study period). Rates of all adverse events and serious adverse events were reported as the number of events in each country per gFe per million inhabitants.

Additionally, data from a subset of specific countries were analyzed separately to determine relative risks for adverse events associated with individual IV iron products, if the countries had both of the following criteria: at least 2 different iron products in use and more than 1 serious allergic adverse event within the study period. Using the composite data for these specific countries, mean values were determined for each product for amount of iron use (gFe/mil), numbers of all adverse events and serious allergic adverse events, and rates of all adverse events and serious allergic adverse events (gFe/mil). Odds ratios (ORs) for the risks of all adverse events or serious allergic adverse events from one product compared to another were calculated in a 2 × 2 table using the numbers of all adverse events or serious allergic adverse events and the amount of iron used per million inhabitants. ORs were reported with 95% confidence intervals, and statistical significance was tested using a Chi-square. A P value of less than .05 was considered statistically significant.

Results

The populations of countries ranged from 1.3 million for Estonia to 299.1 million for the United States, with total populations of 476.5 million for all 16 European countries, 331.7 million for North America, and 808.2 million for all countries combined.

Table 1 indicates the numbers of all adverse events for each product by year. There was a trend towards increasing numbers of annual reports of adverse events, from 154 in 2003 to 560 in 2008. Data from the first 6 months of 2009 (316 events) suggest continued increases in reports. Changes to the software in the WHO database, however, resulted in some of the 2007 reports being recorded in 2008 and thereby potentially skewing the 2007 data downward and the 2008 data upward. The total numbers of adverse events for each product were similar (ranging from 466–606 reports) despite large differences in the amount of each iron used (previously reported). There were no reports of adverse events for iron sucrose similars.

Total IV iron use was 228,427 gFe/mil; however, this was highly impacted by 2 countries—Switzerland and Italy—which together generated 36% of total iron use. Iron sucrose was used in all countries, sodium ferric gluconate in 8 countries, iron dextran in 12, and iron sucrose similars in 3 (Tables 2 and 3). For countries that did use a particular product, inter-country use of the product varied considerably. The use of iron sucrose ranged from 7 gFe/mil (Ireland) to 34,769 gFe/mil (Switzerland); the use of sodium ferric gluconate ranged from 1 gFe/mil (Poland) to 48,674 gFe/mil (Italy, where an undefined proportion of sodium ferric gluconate use is oral); the use of iron dextran ranged from 1 gFe/mil (Switzerland) to 4,581 gFe/mil (United States); and the use of iron sucrose similars ranged from 239 gFe/mil (France) to 2,173 gFe/mil (Spain) over the 6.5-year period.

Many countries had low or no reports of adverse events despite substantial iron use. Thus, rates of all adverse events and serious allergic adverse events reported for each product varied considerably by country (Tables 2 and 3). For example, rates of all and serious allergic adverse events for iron sucrose ranged from 0 (Poland, Austria, and Czech Republic) to 1,222 × 10⁻³ reports/gFe/mil (Ireland) and from 0.2 × 10⁻³ (Finland) to 2.7 × 10⁻³ reports/gFe/mil (Germany), respectively; rates of all and serious allergic adverse events for sodium ferric gluconate ranged from 3.3 × 10⁻³ (Czech Republic)

<table>
<thead>
<tr>
<th>Intravenous Iron Product</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron dextran (combined)</td>
<td>81</td>
</tr>
<tr>
<td>Sodium ferric gluconate</td>
<td>39</td>
</tr>
<tr>
<td>Iron sucrose‡</td>
<td>34</td>
</tr>
<tr>
<td>Total</td>
<td>154</td>
</tr>
</tbody>
</table>

Note: The table includes data for all 16 European countries and North America.

*Due to software changes at the World Health Organization, most 2007 reports were entered into the system in 2008.
†2009 only covers the period of January through June.
‡There were no separate reports for iron sucrose similars.
to $183.6 \times 10^{-3}$ reports/gFe/mil (United States) and from $1 \times 10^{-3}$ (Austria, Czech Republic) to $90 \times 10^{-3}$ reports/gFe/mil (United States), respectively. Rates of all and serious allergic adverse events for iron dextran ranged from $0.9 \times 10^{-3}$ (Turkey) to $46,875 \times 10^{-3}$ reports/gFe/mil (Switzerland) and from $0.9 \times 10^{-3}$ (Turkey) to $47 \times 10^{-3}$ reports/gFe/mil (United Kingdom), respectively. There were no reports that differentiated iron sucrose similars from iron sucrose, and therefore no separation of adverse events could be provided for iron sucrose similars.

There was little consistency between countries for the rates of reported adverse events for any one IV iron product: some countries had very low reported rates of adverse events for a particular product, whereas other countries had high rates. For example, Turkey had a reported total adverse event rate of less than $1.0 \times 10^{-3}$ reports/gFe/mil for iron dextran, whereas Switzerland’s rate for the same product exceeded $46,000 \times 10^{-3}$ reports/gFe/mil. Rates of reports for different products also varied considerably within a specific country. For example, in Germany, there were $8.6 \times 10^{-3}$ total reports/gFe/mil for sodium ferric gluconate, approximately $30 \times 10^{-3}$ total reports/gFe/mil for iron sucrose, and $336 \times 10^{-3}$ total reports/gFe/mil for iron dextran. Alternatively, the United States had the highest rate for iron dextran ($276 \times 10^{-3}$ reports/gFe/mil), intermediate for sodium ferric gluconate ($183 \times 10^{-3}$ reports/gFe/mil), and lowest for iron sucrose ($43 \times 10^{-3}$ reports/gFe/mil).

Figure 1 shows the rates of serious allergic adverse events/gFe/mil by IV iron product and continent. In
In general, the reported rates of serious allergic adverse events for any IV iron product were higher in North America than in Europe. Overall, the reported rates of serious allergic adverse events were highest for iron dextran and lowest for iron sucrose.

Six countries (Germany, Sweden, Turkey, United Kingdom, Canada, and United States) each used at least 2 different iron products during the study period, and reported serious adverse events. Table 4 indicates the mean values of iron use for each product and the numbers and rates of all adverse events and serious allergic adverse events. The rates of all adverse events were lowest for iron sucrose (39.8 × 10⁻³ reports/gFe/mil), intermediate for sodium ferric gluconate (54.8 × 10⁻³ reports/gFe/mil), and highest for iron dextran (337.7 × 10⁻³ reports/gFe/mil). Rates of serious allergic adverse events were also lowest for iron sucrose (1.7 × 10⁻³ reports/gFe/mil), intermediate for sodium ferric gluconate (4.5 × 10⁻³ reports/gFe/mil), and highest for iron dextran (20.5 × 10⁻³ reports/gFe/mil).

The OR and statistical comparisons of risks for all adverse events and serious allergic adverse events are shown in Table 5. Iron sucrose had a significantly lower risk for all adverse events (OR, 0.63; \( P < .0001 \)) or serious allergic adverse events (OR, 0.31; \( P = .001 \)) compared to sodium ferric gluconate. Iron sucrose also had a significantly lower risk for all adverse events (OR, 0.13; \( P < .0001 \)) or serious allergic adverse events (OR, 0.07; \( P < .001 \)) compared to iron dextran.
Sodium ferric gluconate had lower risks for all adverse events (OR, 0.20; \(P<.0001\)) and serious allergic adverse events (OR, 0.24; \(P<.0001\)) compared to iron dextran.

**Discussion**

To our knowledge, this paper represents the first comparison of adverse event rates of IV iron products in different countries, including an analysis by population at risk. Previous studies have demonstrated that changing trends in iron prescribing practices are associated with changes in rates of reported adverse events.\(^1^4\)-\(^1^7\) However, such studies have been unable to examine IV iron use by country or to show the relative use of iron products within and between countries. This current study sheds light upon the relative use of IV iron within populations, and shows interesting and extensive differences in practices.

There is considerable variation in the choice of iron product used by country, with some countries demonstrating substantial preferences for one particular product over others (eg, iron sucrose is predominantly chosen by Austria, Denmark, Finland, France, Norway, Poland, Spain, Sweden, Switzerland, Turkey, and the United Kingdom; sodium ferric gluconate has most use in the Czech Republic, Germany, and Italy; and iron dextran is the most common choice in Ireland and Canada). The reasons for this are unclear, but may be influenced by national formularies, local practices, and regional commercial agreements and marketing strategies. Additionally, geographic differences may be influenced by cultural expectations of care, prescribers’ adherence to international and regional clinical practice guidelines, and perhaps different mixes of patient types that might receive IV iron.

There is also a sizeable variation in the amount of iron that is used from country to country, as standardized by grams of iron sold per million inhabitants (ranging from 1,674 gFe/mil in Ireland to 48,808 gFe/mil in Italy). The reasons for this are also unclear.

Interestingly, some countries have reported adverse events to products that are not sold in those countries (eg, Austria and Switzerland to sodium ferric gluconate and Denmark and Finland to iron dextran). It is possible that these countries may have imported the products from other countries, or that some of these products may be sold directly to hospitals without recording these sales at IMS (eg, tender business). There were no reports of any adverse events for iron sucrose similars. There are several potential explanations, including the possibility that there were indeed no such adverse events. This explanation seems implausible given animal data demonstrating that iron sucrose similars have an increased risk of causing biochemical, histologic, and functional adverse events compared to the originator.\(^1^8\),\(^1^9\) It is more credible that any adverse events observed by clinicians associated with iron sucrose similars were reported only as iron sucrose. Thus, the importance of inclusion of brand names within an adverse event report must be emphasized in order to be able to differentiate any signals arising from these types of product, as recently suggested.\(^1^6\)

### Table 4. Total Iron Use and Correlating Adverse Events and Serious Allergic Adverse Events in January 2003–June 2009 for Countries That Used More Than 1 Iron Product

<table>
<thead>
<tr>
<th>Iron Use</th>
<th># All AE</th>
<th>All AE Rate</th>
<th># SAE</th>
<th>SAE Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron sucrose</td>
<td>7,616.1</td>
<td>193.2</td>
<td>39.8</td>
<td>10.33</td>
</tr>
<tr>
<td>Sodium ferric gluconate</td>
<td>7,436.5</td>
<td>298.8</td>
<td>54.8</td>
<td>32.67</td>
</tr>
<tr>
<td>Iron dextran</td>
<td>1,659.8</td>
<td>337.7</td>
<td>190.7</td>
<td>30.83</td>
</tr>
</tbody>
</table>

Iron use=grams of iron per million inhabitants.

AE rate=number of all adverse events per grams of iron used per million inhabitants (\(\times 10^{-3}\)).

SAE rate=number of serious allergic adverse events per grams of iron used per million inhabitants (\(\times 10^{-3}\)).

*Germany, Sweden, Turkey, the United Kingdom, Canada, and the United States were the 6 countries that used more than 1 iron product.

### Table 5. Odds Ratios for Comparison of All Adverse Events and Serious Allergic Adverse Events by Intravenous Iron Product

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Odds Ratio (95% CI; (P) Value)</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron sucrose versus sodium ferric gluconate</td>
<td>0.63 (0.52–0.76; (P&lt;.0001))</td>
<td>0.31 (0.14–0.65; (P=.001))</td>
</tr>
<tr>
<td>Iron sucrose versus iron dextran</td>
<td>0.13 (0.10–0.15; (P&lt;.0001))</td>
<td>0.07 (0.03–0.15; (P&lt;.0001))</td>
</tr>
<tr>
<td>Sodium ferric gluconate versus iron dextran</td>
<td>0.20 (0.17–0.23; (P&lt;.0001))</td>
<td>0.24 (0.14–0.40; (P&lt;.0001))</td>
</tr>
</tbody>
</table>

AE=adverse events; CI=confidence intervals; SAE=serious allergic adverse events.
Interesting insight was obtained when we compared those 6 countries each using at least 2 different products and reporting at least 1 severe adverse event (Germany, Sweden, Turkey, the United Kingdom, Canada, and the United States). These countries had a combined population of 557.4 million inhabitants (69% of the total population across all countries) and used a total of 78,973 gFe/mil (34.6% of 228,427 gFe/mil total iron use). Table 4 indicates a similar trend for all adverse events and serious allergic adverse events, where the lowest rates were for iron sucrose, intermediate rates were associated with sodium ferric gluconate, and iron dextran had the highest rates. ORs demonstrated a 37% reduced risk of all adverse events, a 69% reduced risk of serious allergic adverse events with iron sucrose compared to sodium ferric gluconate, and reduced risks of 87% and 93%, respectively, compared to iron dextran. Sodium ferric gluconate also had significant reductions in risk for both adverse events compared to iron dextran (Table 5).

Limitations are inherent in studies such as this. Databases are only as accurate and complete as the reports that are delivered to them. There are substantial risks for under-reporting, and the risks of the Weber effect and clinician bias towards over-reporting are also well recognized. The inability of databases to differentiate reports relating to iron sucrose similars from the originator product is worrisome, as it minimizes the detection of a potential signal. This might also become problematic in the United States due to the recent introduction of generic/similar sodium ferric gluconate. Further, sales figures may not necessarily accurately reflect actual administrations of each product—some products might regularly be administered at small doses (e.g., 62.5 mg for sodium ferric gluconate), whereas iron dextran might be administered at doses of 1,000 mg or more. Labeling for any product may also vary from country to country (e.g., sodium ferric gluconate is approved for doses of 62.5 mg in Europe and 125 mg in the United States; iron sucrose is approved at doses of 200 mg in the United States and 500 mg doses in Germany). Moreover, we have combined data for low- and high-molecular-weight iron dextran from the United States and compared this to the low-molecular-weight iron dextran data from Europe. The exact effect of this approach is unclear, particularly since previous reports have suggested that high-molecular-weight products pose a higher risk of adverse events. Further, the type of facility and the type of patient might well influence the results. For example, reports could have originated from clinics, hospitals, or other institutions, and the exact method of administration of agents in those sites might differ. Over the course of the study period, more non-nephrology specialists are likely to have started using IV iron, and it is plausible that different patient disease characteristics and demographics could also impact their responses to IV iron. Thus, caution should be exercised in the generalized interpretation of the results. Nevertheless, pharmacovigilance and the use of spontaneous reporting databases are legitimate means of assessing epidemiologic adverse event data, and can be used to compare rare signals of events.

Our analysis of risks accounting for population is a novel approach. This method has provided insight into the magnitude of iron use by country, and invokes challenging questions about differences in clinical practices between countries. Further, it suggests that there is significant under-reporting of serious allergic adverse events in some countries. Assuming that the real risk for a serious adverse event remains constant from individual to individual, then all countries should demonstrate similar rates of events for any particular product. Exact reasons for these discrepancies should be investigated, but they may be due to national reporting procedures and regulations.

Conclusions

There was considerable international variation in both iron use and choice of product and in rates of all adverse events and serious allergic adverse events reported for each product. For those countries that used at least 2 different iron products in the study period and reported serious allergic adverse events, the rates of all adverse events were smallest for iron sucrose, intermediate for sodium ferric gluconate, and greatest for iron dextran. Rates of serious allergic adverse events were also lowest for iron sucrose, intermediate for sodium ferric gluconate, and highest for iron dextran. Iron sucrose had a significantly lower risk for all adverse events or serious allergic adverse events compared to sodium ferric gluconate and also had a significantly lower risk for all adverse events or serious allergic adverse events compared to iron dextran. Sodium ferric gluconate had lower risks for both all adverse events and serious allergic adverse events compared to iron dextran.

Based on our suspicions regarding differential adverse event rates with similars versus originators, we urge clinicians to also report adverse events by trade name.

Acknowledgment

The authors thank Robert Geldof, Vifor Pharma, Ltd., and Anders Viklund, UMC, who provided substantial assistance with interpretation of the data, some of which were presented at the American Society of Nephrology annual meeting, Denver, Colorado, USA, November 2010.

Conflicts of Interest

This study was supported by a grant from Vifor Pharma, Ltd. Vifor Pharma Ltd. provided input into the design, interpretation of data, and review of the manuscript. Final
decisions regarding study design, data interpretation, and manuscript development and submission were performed solely by the authors. Dr. George Bailie has been or is currently a consultant for Vifor Pharma, Luitpold Pharmaceuticals, Fresenius Medical Care-North America, Genzyme, and Mitsubishi. Jan-Jaap Verhoef has completed an internship at Vifor Pharma, Ltd.

Disclaimer
The information contained in this article does not necessarily represent the opinion of the WHO.

References